UNITED STATES UTILITY PATENT APPLICATION

OF

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FOR

MACHINE PERFUSION SOLUTION FOR ORGAN AND BIOLOGICAL TISSUE PRESERVATION

MACHINE PERFUSION SOLUTION FOR ORGAN AND BIOLOGICAL TISSUE PRESERVATION

Reference to Related Application

[0001] This application claims the benefit of U.S. Provisional Application No. 60/240,024 filed on October 13, 2000, entitled "Organ and Biological Tissue Preservation Machine Perfusion Solution," which is incorporated herein by reference.

Field of Invention

[0002] The invention relates to the field of organ and biological tissue preservation. In particular, the invention relates to machine perfusion solutions for the preservation of organs and biological tissues for implant.

Background of Invention

[0003] It is believed that the ability to preserve human organs for a few days by cold storage after initial flushing with an intracellular electrolyte solution or by pulsatile perfusion with an electrolyte-protein solution has allowed sufficient time for histo-compatibility testing of donor and recipient. It is also believed that preservation by solution or perfusion has also allowed for organ sharing among transplant centers, careful preoperative preparation of the recipient, time for preliminary donor culture results to become available, and vascular repairs of the organ prior to implantation.

[0004] It is believed that the 1990's has been a decade characterized by increasing waiting times for cadaveric organs. In renal transplantation, the growing disparity between available donors and patients on the waiting list has stimulated efforts to maximize utilization of cadaveric organs. An obstacle that may arise in the effort to increase utilization is that maximal utilization may require transplantation of all available organs, including extended criteria donor organs. However, by extending the criteria for suitability of donor organs, transplant clinicians may risk a penalty with respect to graft function, diminishing the efficiency of organ utilization if transplanted organs exhibit inferior graft survival. Consequently, interventions that both

improve graft function and improve the ability of clinicians to assess the donor organ may be crucial to achieving the goal of maximizing the efficiency of cadaveric transplantation.

[0005] The mechanisms of injuries sustained by the cadaveric renal allograft during pre-preservation, cold ischemic preservation and reperfusion are believed to be complex and not fully understood. However, it is believed that there exists ample evidence to suggest that many of the injurious mechanisms occur as a result of the combination of prolonged cold ischemia and reperfusion (I/R). Reperfusion alone may not be deleterious to the graft, since reperfusion after short periods of cold ischemia may be well-tolerated, but reperfusion may be necessary for the manifestation of injuries that originate during deep and prolonged hypothermia. It is suggested that four major components of I/R injury that affect the preserved renal allograft begin during cold ischemia and are expressed during reperfusion. These include endothelial injury, leukocyte sequestration, platelet adhesion and increased coagulation.

[0006] Hypothermically-induced injury to the endothelium during preservation may lead to drastic alterations in cytoskeletal and organelle structures. During ischemic stress, profound changes in endothelial cell calcium metabolism may occur. These changes may be marked by the release of calcium from intracellular depots and by the pathological influx of calcium through the plasma membrane. Hypothermic preservation may disrupt the membrane electrical potential gradient, resulting in ion redistribution and uncontrolled circulation of Ca++. The depletion of ATP stored during I/R may compromise ATP-dependent pumps that extrude Ca++ from the cell and the energy intensive shuttle of organelle membranes, causing a dramatic elevation of intracellular free Ca++.

[0007] Alterations in cytosolic Ca++ concentration may disrupt several intracellular functions, many of which may result in damaging effects. Unregulated calcium homeostasis has been implicated in the development of endothelial and parenchymal injury and is believed to be a fundamental step in the sequelae of steps leading to lethal cell injury. Among the most significant damaging effects of increased cytosolic Ca++ are believed to be the activation of phospholipase A1, 2 and C, the cytotoxic production of reactive oxygen species by macrophages,